The Developmental Toxicity of Perfluoroalkyl Acids and Their Derivatives

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Perfluoroalkyl acids (PFAA) and their derivatives, such as perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA), are surfactants that have wide applications in industrial and consumer products. These chemicals are stable and persist in the environment, but have previously been viewed as biologically inactive. However, recent bio-monitoring studies have indicated widespread prevalence of PFOS and PFOA in humans and wildlife, and preliminary studies have suggested reproductive and developmental toxicities of these chemicals in laboratory animals. These findings have drawn considerable interest from the public, and their relevance to human health risk has rendered this class of chemicals an emerging concern for the program offices at EPA. In response to a call for assistance from OPPTS, our laboratories have partnered with NERL and 3M to characterize the reproductive and developmental toxicity profiles for PFOS (and, more recently, for PFOA) in rodent models and have made significant progress in identifying the possible modes of action for these perfluorinated compounds. Exposure of PFOS during pregnancy produced significant maternal toxicity in both rat and mouse, leading to a reduction of circulating thyroid hormones, a lag of maternal weight gain, and, particularly in the mouse, liver enlargement (suggestive of hepatotoxicity); these effects were directly correlated to body burdens of the chemical. In contrast, little deleterious effects of PFOS were detected on the embryonic and fetal development, and neonates were born alive. However, in a dose-dependent manner, newborn pups exposed to PFOS *in utero* became moribund and died in the ensuing hours to days after birth. Results from our studies indicated that immaturity of the lung and pulmonary function in the PFOS-exposed pups were involved in the neonatal mortality. Deficits of thyroid hormones in circulation were also seen in the surviving pups. Similar results were obtained in the mouse. Because of these findings, toxicological evaluations have recently been extended to PFOA. Unlike humans, the female rat has a unique ability to excrete PFOA efficiently, thus rendering interpretation of reproductive findings with this species confounding. Alternatively, we have examined the effects of PFOA in the mouse and noted an increase of neonatal mortality as well as delays of postnatal development, reminiscent of the PFOS effects. These findings thus suggest the potentials of developmental toxicity for PFAA, and various analogs of PFAA (different functional derivatives and carbon-chain lengths) may share some common features of the adverse outcomes. Hence, a fuller description of their hazards and a better understanding of the mechanisms of their toxicity should provide a sound basis for risk assessment of this entire class of chemicals.